

Application Serial No. 09/684,383  
Supplemental Amendment dated 18 November 2003

#### REMARKS

Claim 24 has been amended to delete the propeptide portion of the protein (SEQ ID NO:2) encoded by SEQ ID NO:1, i.e., the protein encoded by nucleotides 128-835 of SEQ ID NO:1, and the propeptide portion of the protein (SEQ ID NO:4) encoded by SEQ ID NO:3, i.e., the protein encoded by nucleotides 131-838 of SEQ ID NO:3. Claims 25, 29 and 35 have been amended to delete reference to "a part" of the protein in order to clarify the language of the claims so that it is clear that the claims are directed to the mature protein, to which the "part" of the protein referred and was defined in the previously presented claims.

It is submitted that none of these amendments constitute new matter, and their entry is requested.

In the telephone interview with the Examiner, the Examiner questioned the activity of the small proteins set forth in claim 24, e.g., a protein encoded by nucleotides 836-1183 of SEQ ID NO:1. Applicants note that the protein encoded by SEQ ID NO:1 (as set forth in SEQ ID NO:2) encodes a propeptide. The mature protein portion of the protein begins with any one of amino acids 217-240 and ends with amino acid 352 of SEQ ID NO:2 as described in the specification and in the previous amendment. The propeptide portion of the protein begins with amino acid 1 and ends with any one of amino acids 216-239. Nucleotides 836-1183 of SEQ ID NO:1 encodes a mature protein comprising amino acids 237-352 of SEQ ID NO:2. Nucleotides 866-1183 of SEQ ID NO:1 encodes a mature protein having a 10 amino acid truncation at the N-terminus. Similarly, nucleotides 839-1186 of SEQ ID NO:3 encodes a mature protein comprising amino acids 237-352 of SEQ ID NO:4. Nucleotides 869-1186 of SEQ ID NO:3 encodes a mature protein having a 10 amino acid truncation at the N-terminus.

A protein which is the mature protein or which includes the mature protein has the mitogenic and/or differentiation-inductive activity as disclosed in the present application. Since the propeptide portion alone, e.g., the protein encoded by nucleotides 128-835 of SEQ ID NO:1, does not have this activity, it has been deleted from claim 24. With respect to the proteins comprising the mature proteins with a 10 amino acid deletion at the N-terminus, a skilled artisan reasonably expects these truncated proteins to have the specified activity, since they include the seven conserved cysteine

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region. The meaning of the seven conserved cysteine region was known to a skilled artisan at the priority date of the present application. It was also known at the priority date of the present application that truncation of amino acids at the N-terminus for several members of the TGF- $\beta$  superfamily did not affect the activity of the protein. For example, published international application WO 89/09787 discloses that BMP-2 (CBMP-2a), BMP-4 (CBMP-2b) and BMP-7 (OP-1) which start with the first of the seven conserved cysteines and contain the seven conserved cysteine regions are active. The proteins encoded by nucleotides 866-1183 of SEQ ID NO:1 and 869-1186 of SEQ ID NO:3 start with the first conserved cysteine. Thus, a skilled artisan would expect the mature proteins and the truncated proteins to have activity.

In view of the above amendments and remarks, in conjunction with the remarks made in the previous amendment, it is believed that the claims satisfy the requirements of the patent statutes and are patentable over the prior art. Reconsideration of the instant application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,

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